REMARKS

In a non-final Office Action dated August 15, 2006 the Examiner in charge of the above-noted application rejected Claims 1-12 and 17 under 35 USC 112, first paragraph. Claims 13-16 are withdrawn from consideration for being directed to non-elected subject matter. Applicants respond by submitting a second Supplemental Declaration of Dr. Alan Attie and the comments set forth hereinbelow. Accordingly, applicants request reconsideration of the merits of this patent application.

Rejection under 35 U.S.C. §112

Claims 1-12 and 17 stand rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner asserts that

> "[A]lthough Applicants have demonstrated that delivering a plasmid construct encoding LDLR354 and KDEL can lower LDL level in a mouse deficient of LDLR 48 hours post injection, whether such treatment would result in any therapeutic response in human is still unpredictable because the specification fails to demonstrate whether sustained expression maybe maintained at sufficient level to lower LDL for longer period of time." (See page 5, of the current Office Action).

In response, applicants respectfully disagree with the Examiner's assertion. Being that the sole ground for rejection in the above-identified patent application is lack of enablement, submitted with this response is a second Supplemental Declaration of Alan D. Attie, one of the inventors of the present patent application. Applicants also submit herewith, in a Supplemental Information Disclosure Statement, research articles referred to in Dr. Attie's Declaration.

Dr. Attie's Declaration is intended to establish that (1) the mouse is a suitable animal model to mimic human disease in the field of cholesterol research; and (2) a genetic construct can be stably integrated into the genome of a mammal to achieve sustained protein expression to lower serum cholesterol levels. As such, it is believed that the submission of this Declaration will obviate the enablement rejection applied by the Examiner against the claims of this patent application.

Specifically, paragraphs 4-6 of Dr. Attie's Declaration outlines several reasons why mouse data is predictive of a human therapeutic response in lowering serum cholesterol levels for a longer period of time. Dr. Attie declares that the mouse is the most widely used

animal model in lipoprotein research (see Breslow, J.L. (1993) *Proc Natl Acad Sci U S A* 90:8314-8318; De Winther, M.P., and Hofker, M.H. (2002) *Curr Opin Lipidol* 13:191-197; and Marschang, P., and Herz, J. (2003) *Semin Cell Dev Biol* 14:25-35). Dr. Attie states that in his laboratory they have created common inbred mouse strains to replicate the variable susceptibility of all mammals including human to diabetes and have been successfully mined for pathways and genes relevant to human diabetes (Clee, S.M., and Attie, A.D. (2007) *Endocr Rev* 28:48-83).

In the Declaration, Dr. Attie states that the basic biochemical processes, genes, enzymes, and pathways of the mouse are identical to a human. It is also widely known that by modifying the expression of genes through transgenic technology, mice have been produced that do have similar lipoprotein profiles to humans (See Grass, D.S. et al. (1995) *J Lipid Res* 36:1082-1091; Herrera, V.L. et al., (1999) *Nat Med* 5:1383-1389; Masucci-Magoulas, L., et al., (1997) *Science* 275:391-394; and Takahashi, H., et al., (2001) *Biochem Biophys Res Commun* 283:118-123). For at least these reasons, the mouse is considered a preferred animal model for studying approaches to regulate serum cholesterol levels in humans.

Next, in relation to the Examiner's comments regarding the lack of sustained expression levels beyond 48 hours in mice to lower LDL, Dr. Attie also disagrees, He states in the Declaration that stable integration of genetic material into a genome and sustained expression of the desired protein has been achieved as predicted in the original specification. Dr. Attie asserts that despite some preliminary set backs in gene therapy, great progress has been made with adeno-associated virus (AAV) (see Warrington, K.H., Jr., and Herzog, R.W. (2006) *Hum Genet* 119:571-603.) Dr. Attie states that this virus can support long-term expression without causing an inflammatory response that is commonly associated with adenovirus. To support this assertion, the Declaration refers to a recent publication where AAV gene therapy was used to deliver a human lipoprotein lipase (LPL) variant to LPL-deficient mice (See Rip, J., et al. (2005) *Hum Gene Ther* 16:1276-1286). This therapy was able to normalize the dyslipidemia of the mice for more than one year. Dr. Attie also notes that preliminary studies were done in human subjects to show that they express the

transduced gene in muscle biopsies, which is a prelude to clinical trials evaluating its efficacy for lowering lipids in human subjects.

Wherefore reconsideration of the merits of this patent application in view of this submission is requested. Accordingly, it is requested that a timely Notice of Allowance be issued in this case.

A separate petition for a three-month extension of time is enclosed so that this response will be considered as timely filed. Accompanying this response is a Second Supplemental Declaration and a supplemental Information Disclosure Statement. No other fees are believed due in regard to this submission. If any other fee is due or any other extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to the Deposit Account No. 17-0055.

Respectfully submitted,

Sara D. Vinarov
Reg. No. 48,524
Attorney for Applicants
QUARLES & BRADY LLP
P.O. Box 2113
Madison, WI 53701-2113

TEL (608) 251-5000
FAX (608)251-9166